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Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis

Nurmatov, Ulugbek ; Dhami, Sangeeta ; et al

Abstract: Background: The European Academy of Allergy and Clinical Immunology (EAACI) is developing Guidelines for Allergen Immunotherapy (AIT) for IgE-mediated Food Allergy. To inform the development of clinical recommendations, we sought to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT in the management of food allergy. Methods: We undertook a systematic review and meta-analysis that involved searching nine international electronic databases for randomized controlled trials (RCTs) and non-randomized studies (NRS). Eligible studies were independently assessed by two reviewers against pre-defined eligibility criteria. The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and the Cochrane ACROBAT-NRS tool for quasi-RCTs. Random-effects meta-analyses were undertaken, with planned subgroup and sensitivity analyses. Results: We identified 1814 potentially relevant papers from which we selected 31 eligible studies, comprising of 25 RCTs and six NRS, studying a total of 1259 patients. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated sublingual immunotherapy (SLIT) and one study evaluated epicutaneous immunotherapy (EPIT). The majority of these studies were in children. Twenty-seven studies assessed desensitization and nine studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR)=0.19, 95%CI 0.12, 0.29) and sustained unresponsiveness (RR=0.20, 95%CI 0.10, 0.59). Only one study reported on disease-specific quality of life (QoL), which reported no comparative results between OIT and control group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses. Conclusions: AIT may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. It is however associated with a modest increased risk in serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, the impact on QoL and the cost-effectiveness of AIT.

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Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis

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Abstract

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Methods: We undertook a systematic review and meta-analysis that involved searching nine international electronic databases for randomized controlled trials (RCTs) and non-randomized studies (NRS). Eligible studies were independently assessed by two reviewers against pre-defined eligibility criteria. The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and the Cochrane ACROBAT-NRS tool for quasi-RCTs. Random-effects meta-analyses were undertaken, with planned subgroup and sensitivity analyses.

Results: We identified 1814 potentially relevant papers from which we selected 31 eligible studies, comprising of 25 RCTs and six NRS, studying a total of 1259 patients. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated sublingual immunotherapy (SLIT) and one study evaluated epicutaneous immunotherapy (EPIT). The majority of these studies were in children. Twenty-seven studies assessed desensitization and nine studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR)=0.19, 95%CI 0.12, 0.29) and sustained unresponsiveness (RR=0.20, 95%CI 0.10, 0.59). Only one study reported on disease-specific quality of life (QoL), which reported no comparative results between OIT and control

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group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses.

Conclusions: AIT may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. It is however associated with a modest increased risk in serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, the impact on QoL and the cost-effectiveness of AIT.

Keywords: Allergen, allergen immunotherapy, desensitization, food allergy, safety, sensitization, sustained unresponsiveness.

BACKGROUND

Food allergy may result in considerable morbidity and, in some cases, mortality.(1) Epidemiological studies have demonstrated that the prevalence and severity of food allergy may be increasing, particularly in children.(2-8) Food allergies can be divided into IgE-mediated acute allergic reactions manifesting as urticaria, vomiting, wheezing and anaphylaxis, and non-IgE-mediated food allergy which results from delayed, cell-mediated reactions. This systemic review is focused on IgE-mediated reactions.

Food allergies can be associated with significant reduction in disease specific quality of life (QoL) – both of individuals who suffer from food allergy and their family members.(9, 10) At present, avoidance measures are the cornerstone of management.(11) Difficulties in avoiding responsible food allergens can however result in accidental exposure and the risk of triggering potentially life-threatening anaphylaxis. Of concern is the increasing numbers of people being seen in emergency departments or who are hospitalized because of food-induced anaphylaxis.(12, 13) Individuals with food allergy therefore need to carry adrenaline (epinephrine) auto-injectors in order to self-manage anaphylaxis. This approach is however perceived as restrictive and still leaves patients at risk if accidental exposure occurs.(2, 7, 8)

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Allergen immunotherapy (AIT) has been used for over a century to treat those with food allergy.(14) It involves repeated administration of gradually increasing doses of the antigens to which individuals are allergic in the hope of allowing safe exposure to the food(s) in question. Whilst AIT has become an established treatment regimen in relation to the management of, for example, pollen and insect venom allergy,(15) it has yet to become established in the routine management of food allergy.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines for AIT, and this systematic review and meta-analysis is one of five inter-linked assessments of the current evidence base in relation to evaluating AIT for the treatment of food allergy, allergic rhinoconjunctivitis, venom allergy, allergic asthma and allergy prevention, which will be used to inform development of clinical recommendations. The focus of this review, which builds on our previous related reviews,(16, 17) is to assess the effectiveness, safety and cost-effectiveness of AIT in the management of IgE-mediated food allergy.

METHODS

Details of the methods employed in this review, including search terms and filters, databases searched, inclusion and exclusion criteria, data extraction and quality appraisal, have been previously reported.(18) We therefore confine ourselves here to a synopsis of the methods employed.

Search strategy

Nine international databases were searched for published material: Cochrane Library, which includes CENTRAL [Trials, Methods studies, Health Technology Assessments (HTA), Economic Evaluation database (EED)]; MEDLINE, EMBASE, ISI Web of Science, TRIP and CINAHL. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Supporting Information - Appendix 1, search strategies 1 and 2). Our database searches covered from inception to March 31, 2016. The bibliographies of all eligible studies were scrutinized to identify additional possible studies. No language restrictions were imposed and where necessary manuscripts were translated into English.

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Inclusion criteria

Patient characteristics

We focused on studies conducted on children and adults of any age with a clinician-diagnosed IgE-mediated food allergy to milk, eggs, peanuts, tree nuts and other foods with confirmation of allergic status through positive skin prick tests, specific-IgE and/or food challenge tests.

Interventions of interest and comparators

This review focused on AIT for different allergens, i.e. milk, eggs, tree nuts, peanuts and other foods, administered through the following routes: oral (OIT), sublingual (SLIT) and epicutaneous (EPIT). We were interested in studies comparing food allergy AIT with placebo or routine care (i.e. adrenaline auto-injector with or without antihistamines) or no treatment.

Outcomes

Our primary outcomes of interest were: 1) desensitization (i.e. the ability to safely consume foods containing the allergen in question while on AIT); 2) sustained unresponsiveness (i.e. the ability to safely consume foods containing the allergen in question after discontinuing AIT) at food challenge; and 3) changes in disease specific QoL using a validated instrument. Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the World Allergy Organization's (WAO) grading system of side-effects.(19, 20)

Study designs

We were interested in RCTs investigating the role of OIT, SLIT or EPIT in children and adults with IgE-mediated food allergy. However, given the likelihood that we would find only a limited number of RCTs, we also searched for non-randomized studies (NRS), these including non-randomized controlled clinical trials (CCTs), controlled before-and-after (CBA) studies and interrupted time series (ITS) analyses.

Study selection

All references were uploaded into the systematic review software DistillerSR. Titles and abstracts of identified studies were checked and independently reviewed by two researchers (UN, SD). The full text of all potentially eligible studies were assessed for eligibility against the eligibility criteria (UN, SA). Any disagreements were resolved through discussion, with SD or AS arbitrating if agreement could not be reached.

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Quality assessment strategy

The quality of included RCTs was independently assessed by two reviewers (UN, SA) using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of Interventions.(21) Critical appraisal of quasi-RCTs, CCTs was undertaken using the Cochrane ACROBAT tool for NRS.(22) An overall assessment of quality for each trial using these categories was arrived at through consensus discussion amongst reviewers.

Data extraction, analysis and synthesis

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA) and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS).

Where possible and appropriate, data were synthesized using random-effects meta-analyses following the pre-specified analysis plan. For the assessment of safety, as there were a number of studies with zero reported outcomes, in order to facilitate meta-analyses we expressed safety data as the risk of not experiencing a local or systemic reaction. All analyses were undertaken using the software Comprehensive Meta-Analysis (version 3).

Sensitivity, subgroup analyses, and assessment for publication bias

Sensitivity analyses were undertaken by focusing on results from double-blind RCTs. Subgroup analyses were undertaken to compare:

- Diagnosis of food allergy was confirmed by double-blind, placebo-controlled, food challenge (DBPCFC) versus without DBPCFC
- Route of administration: OIT versus SLIT versus EPIT
- Children (0-17 years) versus adults (≥18 years)
- Type of AIT protocol: conventional versus rush
- Allergens used for AIT.

Where possible, publication bias was assessed through the creation of funnel plots in Comprehensive Meta-Analysis (version 3).

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Registration and reporting of this systematic review

This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) with registration number: CRD42016039384.

RESULTS

Our searches identified 1814 potentially relevant papers, from which we identified 31 trials that satisfied our inclusion criteria studying a total of 1259 patients (Figure 1: PRISMA flow diagram). There were 25 RCTs (23-46) and six NRS', all of which were CCTs.(47-52) Twenty-five of these trials investigated OIT(23-27, 30, 33, 35-50, 52), one epicutaneous immunotherapy (EPIT)(28) and the remaining five investigated SLIT.(29, 31, 32, 34, 51) One report included two independent RCTs on cow's milk (CMA) and hen's egg (HEA).(39) Sixteen studies focused on CMA,(25, 35-37, 39-44, 47-51) 11 on HEA,(24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51) seven on peanut,(23, 32, 34, 45, 46, 50, 52) one hazelnut,(29) two peach,(31, 50) three apple,(41, 50, 51) three fish,(41, 50, 51) and two other studies focused on a variety of food allergens including orange, corn, bean, lettuce,(50) wheat and bean(51) (see Table 1 and Supporting Information: Appendix 2, Table S1). The trials were undertaken in Italy (n=9), Spain (n=7), the USA (n=6), France (n=3), Australia (n=1), Finland (n=1), Germany (n=1), Iran (n=1), Korea (n=1), and the UK (n=1).

Quality assessment

Quality assessment of these studies revealed that eight of the RCTs were judged to be at low risk of bias;(24, 26, 32, 34, 36, 40, 45, 46) a further five RCTs were judged as at unclear risk of bias,(28, 31, 33, 37, 43) and the remaining 12 RCTs(23, 25, 27, 29, 30, 35, 38, 39, 41, 42, 44) were judged to be at high risk of bias (see Supporting Information: Appendix 3, Table S2). The six CCTs(47-52) were all judged to be at moderate risk of bias (see Supporting Information: Appendix 4, Table S3).

Primary outcomes

Desensitization

Desensitization was assessed in 18 OIT RCTs(23-27, 33, 35-43, 45, 46) and five OIT CCTs.(47-51) There were also four SLIT RCTs(29, 31, 32, 34) and one SLIT CCT(51) that assessed desensitization. The efficacy of AIT was compared with placebo in 12 studies, eight of which

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used OIT(24-26, 42, 43, 45, 46) and four of SLIT;(29, 31, 32, 34) the other 17 studies, all of OIT, employed routine care (i.e. food avoidance/strict elimination diet as the comparator).(27, 30, 33, 35-39, 41, 44, 47-52)

Meta-analysis was possible with data from 28 trials investigating a total of 1218 subjects; this revealed a substantial benefit with respect to desensitization: relative risk (RR)=0.19, 95%CI 0.12, 0.29; see Figure 2(a).(23-27, 29-41, 43, 44, 46-52)

Sensitivity analyses

Sensitivity analysis of the 22 RCTs, excluding the six CCTs, also demonstrated a substantial benefit: RR=0.24, 95%CI 0.16, 0.37; see Figure 2(b).(23-27, 29-41, 43, 44, 46) A further sensitivity analysis excluding all trials judged to be at high risk of bias confirmed this substantial benefit: RR=0.15, 95%CI 0.09, 0.24; see Figure 2(c)(24, 26, 31-34, 36, 37, 40, 43, 46-52) A further sensitivity analysis excluding all trials (whether OIT or SLIT) judged to be at high risk of bias demonstrated a substantial average risk reduction (RR OIT=0.17, 95%CI 0.11, 0.26);(24, 26, 33, 36, 37, 40, 43, 46-50) (RR SLIT=0.31, 95%CI 0.10, 0.98)(31, 32, 34) (see Supplementary Materials: Appendix 5, Figures S1 and S2).

A final sensitivity analysis focusing on studies in which desensitization was confirmed by DBPCFC after OIT or SLIT also revealed substantial benefits (RR 0.19, 95%CI 0.12, 0.32; see Supplementary Materials: Appendix 5, Figure S3).(23, 25-27, 29-31, 35-41, 43, 44, 47-52)

Subgroup analyses

- Subgroup analysis based on the route of administration of AIT (OIT versus SLIT) revealed that both OIT (RR=0.17, 95%CI 0.10, 0.27; see Figure 3)(23-27, 30, 33, 35-41, 43, 44, 46-50, 52) and SLIT were effective (RR=0.26, 95%CI 0.10, 0.64; see Figure 4).(29, 31, 32, 34, 51)
- A subgroup analysis based on the age of the population studied (children aged up to 18 years old, adults ≥18 years old and mixed population that included subjects 0-55 years old) revealed a substantial average risk reduction only for children and mixed populations, but not for adults studies (RR, children's studies=0.19, 95%CI 0.12, 0.30)(23-27, 30, 32-41, 43, 44, 46-49)

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- (RR, adults studies=0.56, 95%CI 0.23, 1.36)(29, 31) (RR, mixed population=0.04, 95%CI 0.01, 0.19)(50-52) (see Supplementary Materials: Appendix 5, Figures S4, S5 and S6).
- Subgroup analysis based on the type of AIT protocol (conventional versus rush) also showed a substantial average risk reduction for both methods (RR, conventional protocol=0.12, 95%CI 0.07, 0.21);(23-27, 30, 32-35, 38, 40, 43, 44, 46, 47, 49-52) (RR, rush=0.43, 95%CI 0.27, 0.70)(29, 31, 36, 37, 39, 41, 48) (see Supplementary Materials: Appendix 5, Figures S7 and S8).
- Subgroup analyses of types of allergen demonstrated that in 14 trials investigating CMA, 11 HEA and four peanut allergy OIT/SLIT substantially reduced the risk of desensitization to CMA, HEA and peanut allergy (RR CM=0.16, 95%CI 0.08, 0.32);(25, 35-37, 39-41, 43, 44, 47-51) (RR HE=0.22, 95%CI 0.11, 0.44);(24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51) (RR peanut=0.11, 95%CI 0.04, 0.31)(23, 32, 34, 46) (see Supplementary Materials: Appendix 5, Figures S9, S10 and S11. A sensitivity analysis of the 17 OIT and four SLIT RCTs found a substantial average risk reduction (RR OIT=0.23, 95%CI 0.14, 0.38);(23-27, 30, 33, 35-41, 43, 44, 46) (RR SLIT=0.31, 95%CI 0.13, 0.76)(29, 31, 32, 34) (see Supplementary Materials: Appendix 5, Figures S12 and S13).

The Funnel plot revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Figure 5).

Sustained unresponsiveness post-discontinuation of AIT

There were seven OIT RCTs,(24, 26, 30, 33, 42, 44, 45) and two OIT CCTs(48, 52) that investigated the longer-term effects of AIT between two weeks and 36 months after discontinuation of AIT (see Table 1 and Appendix 2: Table S1). Meta-analysis revealed the benefits of OIT (RR=0.20, 95%CI 0.07, 0.59)(24, 26, 30, 33, 44, 48) (see Figure 6).

A sensitivity analysis focusing on only RCTs in which sustained unresponsiveness was confirmed by DBPCFC after OIT or SLIT also revealed substantial benefits (RR 0.23, 95%CI 0.07, 0.73; see Figure 7).(24, 26, 30, 33, 44)

The Funnel plot also revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Figure 8).

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Disease specific quality of life

Only one OIT RCT reported disease-specific QoL of patients and their families.(23) This study used a validated questionnaire for parents, the Food Allergy Quality of Life Questionnaire Parent Form (FAQLQ-PF) however no comparative results between OIT and the control group were reported at the end of the first phase of the study. Results are reported for the end of the second phase of the study at which time the control group had also received OIT.

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Secondary Outcomes

Safety

Systemic reactions

Data on the occurrence of systemic adverse reactions during AIT were available from 25 trials.(23-27, 29-31, 33, 35, 36, 39, 40, 42-51) (Table 1). However, there were different formats of reporting systemic reactions between trials, and we were therefore only able to pool data from seven studies.(26, 29, 31, 35, 40, 46, 49) Meta-analyses of *not* experiencing a systemic reactions was higher in those receiving control: RR=1.09, 95%CI 1.00, 1.19) (see Figure 9).(26, 29, 31, 35, 40, 46, 49).

Subgroup analysis demonstrated that the risk of experiencing a systemic reactions was higher in those receiving AIT (RR of *not* experiencing a reaction in controls=1.16, 95%CI 1.03, 1.30).(26, 35, 40, 46, 49) In contrast, data from two SLIT studies showed no difference between arms (RR of *not* experiencing a reaction in controls=0.98, 95%CI 0.85, 1.14)(29, 31) (see Supplementary Materials: Appendix 5, Figures S14 and S15).

Sensitivity analysis excluding all trials judged to be at high risk of bias after OIT or SLIT demonstrated either a borderline difference (RR of *not* experiencing a reaction in controls=1.10, 95%CI 0.99, 1.23)(26, 31, 40, 46, 49) or a significant difference in the rate of systemic reactions between the two arms after OIT (RR of *not* experiencing a reaction in controls=1.17, 95%CI 1.03, 1.33)(26, 40, 46, 49) (see Supplementary Materials -Appendix 5, Figures S16 and S17).

A subgroup analysis of CMA trials found that the risk of experiencing a systemic reactions was higher in the AIT arm (RR of *not* experiencing a reaction in controls=1.19, 95%CI 1.03, 1.37)(35, 40, 49) (see Supplementary Materials: Appendix 5, Figure S18). Subgroup analysis of systemic reactions during OIT from five children's studies to cow's milk, egg or peanut showed a significant difference between the two arms, however the pooled data from the two studies with

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adult populations using SLIT for peach or hazelnut allergy found no clear evidence of a difference in systemic reactions between the treatment arms and the control arms (RR of *not* experiencing a reaction in controls, children=1.16, 95%CI 1.03, 1.30);(26, 35, 40, 46, 49) (RR of *not* experiencing a reaction in controls, adult=0.98, 95% CI 0.85, 1.14)(29, 31) The lack of a significant effect in adults may reflect a lack of precision (as the point estimate suggests benefit), which in turn is a function of the paucity of large trials in adult populations.
(see Supplementary Materials: Appendix 5, Figures S19 and S20).

Local reactions

Data on occurrence of local adverse reactions during AIT (minor oropharyngeal/gastrointestinal/ perioral rash) were available from 28 trials.(23-31, 33, 35-51) (see Table 1). However, there were different formats of reporting reactions between trials, and we were therefore only able to pool data from 10 studies. Meta-analyses of local reactions obtained from these 10 trials demonstrated that AIT was associated with an increased risk of local reactions (RR of *not* experiencing a reaction in controls 1.88, 95%CI 1.42, 2.48)(24, 26, 35, 37-40, 49) (see Figure 10).

Subgroup analysis of local adverse events demonstrated higher risk of reactions in those receiving OIT (RR of *not* experiencing a reaction in controls=1.78, 95%CI 1.35, 2.33)(24, 26, 37-40, 49) (see Supplementary Materials: Appendix 5, Figure S21). A further sensitivity analysis excluding all trials judged to be at high risk of bias also showed an increased risk of local reactions in the treatment arms compared with the control arms (RR of *not* experiencing a reaction in controls=2.58, 95%CI 1.37, 4.89)(24, 26, 37, 40, 49) (see Supplementary Materials: Appendix 5, Figure S22). Local reactions during OIT from only RCTs subgroup analysis demonstrated higher risk of local reactions in the AIT group (RR of *not* experiencing a reaction in controls=1.71, 95%CI 1.31, 2.24)(24, 26, 35, 37-40) (see Supplementary Materials- Appendix 5, Figure S23). Another subgroup analysis of local reactions during OIT for CMA from either RCTs and CCTs or only RCTs also demonstrated increased risk of having local reactions in the AIT group (from RCTs and CCTs, RR of *not* experiencing a reaction in controls=2.70, 95%CI 1.33, 5.47);(35, 37, 39, 40, 49) (from RCTs, RR of *not* experiencing a reaction in controls=2.36, 95%CI 1.13, 4.96)(35, 37, 39, 40) (see Supplementary Materials: Appendix 5, Figures S24 and S25). Local reactions during OIT for HEA also found an increased risk of local reactions in the AIT arm (RR of *not* experiencing a reaction in controls=1.55, 95%CI 1.09, 2.22)(24, 26, 38, 39) (see Supplementary Materials: Appendix 5, Figure S26).

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The effect of the AIT protocol (conventional versus rush) on the occurrence of local reactions during the treatment was available only from OIT trials. Both, conventional and rush AIT protocols demonstrated an increased risk of local reactions in the treatment arm compared with the controls (RR of *not* experiencing a reaction in controls, conventional=2.58, 95% CI 1.46, 4.55)(24, 26, 35, 38, 40, 49) (RR of *not* experiencing a reaction in controls, rush=1.39, 95% CI 1.00, 1.94)(37, 39)(see Supplementary Materials: Appendix 5, Figures S27 and S28).

Health economic analysis

None of the studies reported data on cost-effectiveness.

DISCUSSION

Summary of main findings

This systematic review and meta-analysis has found evidence that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. This evidence comes mainly from studies in children and it is therefore still unclear if AIT is effective for adults. Pooling of the safety data demonstrated an increased risk of local and systemic reactions with AIT. No fatalities were reported during AIT. Only one study assessed QoL,(23) which reported no comparative results between OIT and the control group. We found no data investigating the cost-effectiveness of AIT in patients with food allergy.

Strengths and limitations of this work

We believe that this systematic review is the most robust investigation undertaken to date to support the use of AIT in children and adults with food allergy.(53-60) A key strength of our systematic review was the comprehensiveness of the searches. We carefully identified and scrutinized the characteristics of all possible terms, including MeSH, EMTREE and free keywords for different types of food allergy and AIT. In addition, we encompassed all available bodies of evidence from all randomized and NRS, with a range of planned subgroup and sensitivity analyses.

The main limitations of this systematic review stem from the heterogeneity of included populations, interventions, outcomes, diversity of AIT protocols and treatment modalities, and definition of outcomes (e.g. adverse reactions). Due to the heterogeneity of studies, the meta-analyses need to be interpreted with caution. In an attempt to account for this heterogeneity, we

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undertook random-effects meta-analyses which produce more conservative assessments of benefits than would have been obtained using fixed-effects meta-analyses. That said, this is an area that will warrant further exploration of the possible sources of heterogeneity in follow-on work. We were also limited by the lack of data on long-term adverse outcomes (e.g. eosinophilic eesophagitis) and lack of data on cost-effectiveness. Studies which were published after our cut-off date 31st March 2016 are not included in this review which may have provided additional evidence to support the effectiveness and safety of OIT.(61)

Conclusions

We found that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT, but was associated with an increased risk of local and systemic adverse events. Future trials need in particular to investigate the effectiveness of AIT in adults, understand the impact of AIT on disease-specific QoL of patients and family members, and establish the cost-effectiveness of AIT for food allergy.

Conflicts of interest: U Nurmatov, no conflicts of interest; Sangeeta Dhami reports grants from EAACI to carry out the review; S Arasi reports other from Evidence-Based Health Care Ltd during the conduct of the study; G Pajno reports grants from Stallergenes during the conduct of the study; M Fernandez Rivas reports grants from European Union, grants from Instituto de Salud Carlos Ill, Ministerio de Ciencia, Espaha, grants from Ministerio de Economia, Espaha, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, personal fees from ALK Abello, Merck, GSK, non-financial support from EAACI, personal fees and non-financial support from Fundaci6n SEAIC, other from Hospital Clinico San Carlos and Universidad Complutense de Madrid, outside the submitted work; In addition, Fernandez Rivas has a patent PT0042/2013 issued; A Muraro reports personal fees from Novartis , personal fees from Meda Mylan, outside the submitted work; G Roberts has a patent use of sublingual immunotherapy to prevent the development of allergy in at risk infants. issued and his University has received payments for activities he has undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck; C Akdis reports grants from Actellion, personal fees from Aventis, personal fees from Stallergenes, grants and personal fees from Allergopharma, personal fees from Circassia, grants from Novartis, grants from Christine Kuhne Center for Allergy Research and Education, outside the submitted work; Alvaro has nothing to disclose; K Beyer reports grants from DBV, grants and personal fees from Aimmune, outside the submitted work; C Bindslev-Jensen reports grants from Anergis, grants from AImmune, grants from HAL Allergy, outside the submitted work; W Burks reports grants from Food Allergy & Anaphylaxis Network, grants from National Institutes of Health, grants from Wallace Research Foundation, during the conduct of the study; personal fees from FARE, personal fees from NIH AITC Review Panel, personal fees from NIH HAI Study Section, personal fees from World Allergy Organization, personal fees from Aimmune Therapeutics, Inc., personal fees from Epiva Biosciences, Inc., personal fees from Genentech, personal fees from Merck, non-financial support from Regeneron Pharmaceuticals, Inc., personal fees from Stallergenes, personal fees from Valeant Pharmaceuticals North America, LLC, personal fees from PPD Development, LP, personal fees from Allertein, personal fees from Sanofi US Services, outside the submitted work; G Du Toit reports income from grants from National Institute of Allergy and Infectious Diseases (NIAID, NIH), Food Allergy & Research Education (FARE), MRC & Asthma UK Centre, UK Dept of Health through NIHR, National Peanut Board (NPB), and grants from UK Food Standards Agency (FSA); these grants part funded salary over period of this submitted work; M Ebisawa has nothing to disclose; P Eigenmann reports personal fees from DBV technologies, personal fees from Mictotest DX, personal fees from Nestlé, from Gesellschaft zur Förderung der dermatologischen Forschung und Fortbildung e.V., personal fees from Danone, personal fees from Novartis, personal fees from EFSA, grants from Swiss National Science Foundation, grants from Ulrich Muller Gierock Foundation, grants from LETI, grants and personal fees from ThermoFischer, personal fees from Sodilac, personal fees from UpToDate, personal fees from Elsevier, outside the submitted work; E Knol has nothing to disclose; M Mäkelä has nothing to disclose; K C Nadeau has a patent pending; L O'Mahony reports personal fees from Alimentary Health, grants from GSK, outside the submitted work; N Papadopoulos reports personal fees from AbbvieD from Novartis, from GSK, from Novartis, from Faes Farma, from BIOMAY, from HAL, personal fees from MEDA, personal fees from Novartis, personal fees from Menarini, personal fees from ALK ABELLO, personal fees from Novartis, personal fees from CHIESI , personal fees from Faes Farma, personal fees from Uriach , personal fees from Novartis , personal fees from Stallergenes, personal fees from Abbvie, personal fees from MEDA, personal fees from MSD, grants from NESTEC, grants from MERCK SHARP & DOHME, outside the submitted work; L Poulsen reports grants from EU Commission, during the conduct of the study; C Sackesen reports grants from MSD to support laboratory tests for the study 'Effects of the montelukast therapy on asthma and allergic inflammation in children with food allergy, outside the submitted work; H Sampson reports that he is employed 60% of time as Professor of Pediatrics at the Icahn School of Medicine at Mount Sinai and 40% of time as the Chief Scientific Officer at DBV Technologies, which is developing a patch for epicutaneous immunotherapy; A Santos has nothing to disclose; R van Ree reports personal fees from HAL Allergy BV, personal fees from Citeq BV, outside the submitted work; F Timmermans has nothing to disclose; A Sheikh reports grants from EAACI, during the conduct of the study

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Contributorship: AS conceived this review. This paper was drafted by UN, SD and SA. It was revised following critical review initially by AS and then by all the co-authors. This paper is part of the EAACI AIT guidelines project, chaired by Antonella Muraro and coordinated by Graham Roberts.

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Figure 1: PRISMA Flow Diagram

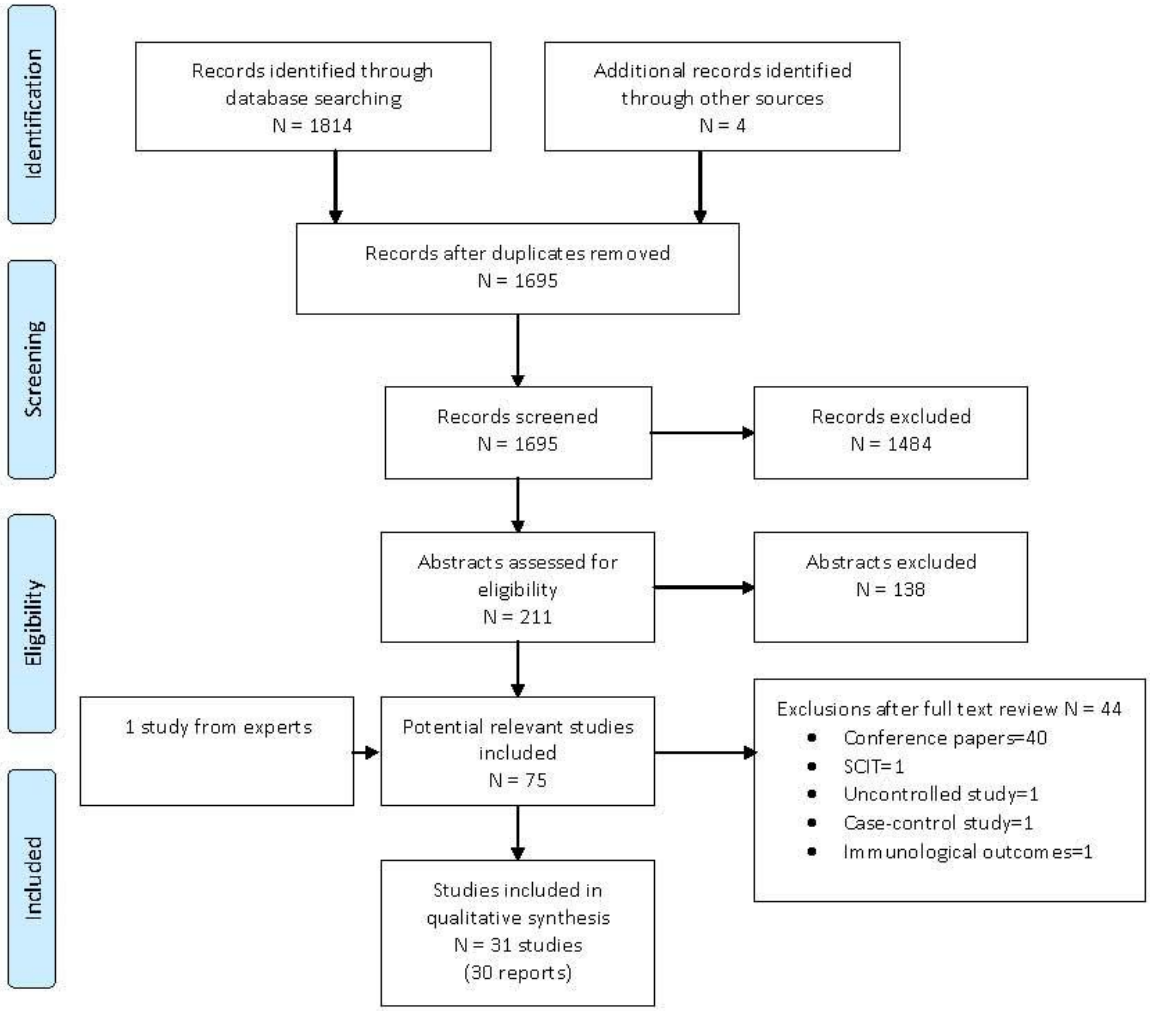

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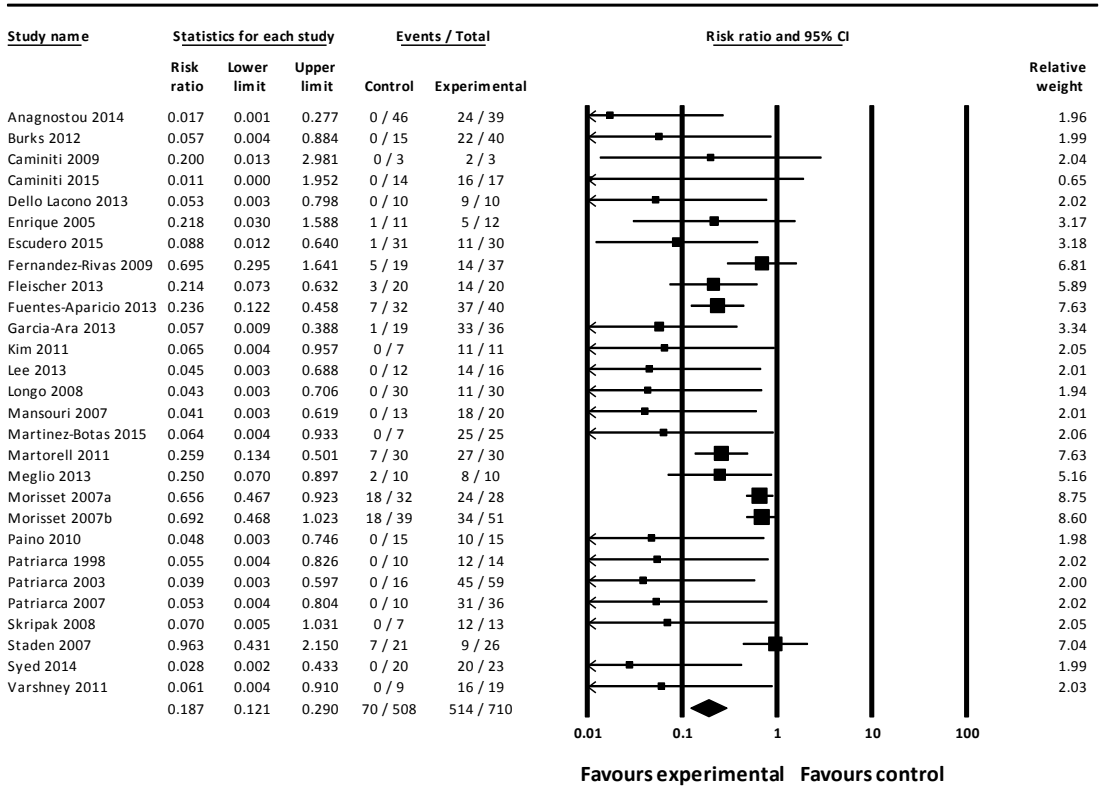
Figure 2(a). Risk ratios (RR) of desensitization following oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) v. controls (random-effects model)



Study name	Statistics for each study			Events / Total		Relative weight
	Risk ratio	Lower limit	Upper limit	Control	Experimental	
Anagnostou 2014	0.017	0.001	0.277	0 / 46	24 / 39	1.96
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	1.99
Caminiti 2009	0.200	0.013	2.981	0 / 3	2 / 3	2.04
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	0.65
Dello Lacono 2013	0.053	0.003	0.798	0 / 10	9 / 10	2.02
Enrique 2005	0.218	0.030	1.588	1 / 11	5 / 12	3.17
Escudero 2015	0.088	0.012	0.640	1 / 31	11 / 30	3.18
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	6.81
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20	5.89
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	7.63
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	3.34
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11	2.05
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	2.01
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	1.94
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	2.01
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	2.06
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	7.63
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	5.16
Morisset 2007a	0.656	0.467	0.923	18 / 32	24 / 28	8.75
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	8.60
Paino 2010	0.048	0.003	0.746	0 / 15	10 / 15	1.98
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	2.02
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	2.00
Patriarca 2007	0.053	0.004	0.804	0 / 10	31 / 36	2.02
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	2.05
Staden 2007	0.963	0.431	2.150	7 / 21	9 / 26	7.04
Syed 2014	0.028	0.002	0.433	0 / 20	20 / 23	1.99
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	2.03
	0.187	0.121	0.290	70 / 508	514 / 710	

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Figure 2(b). Sensitivity analysis RR of desensitization after OIT or SLIT (only randomized controlled trials)

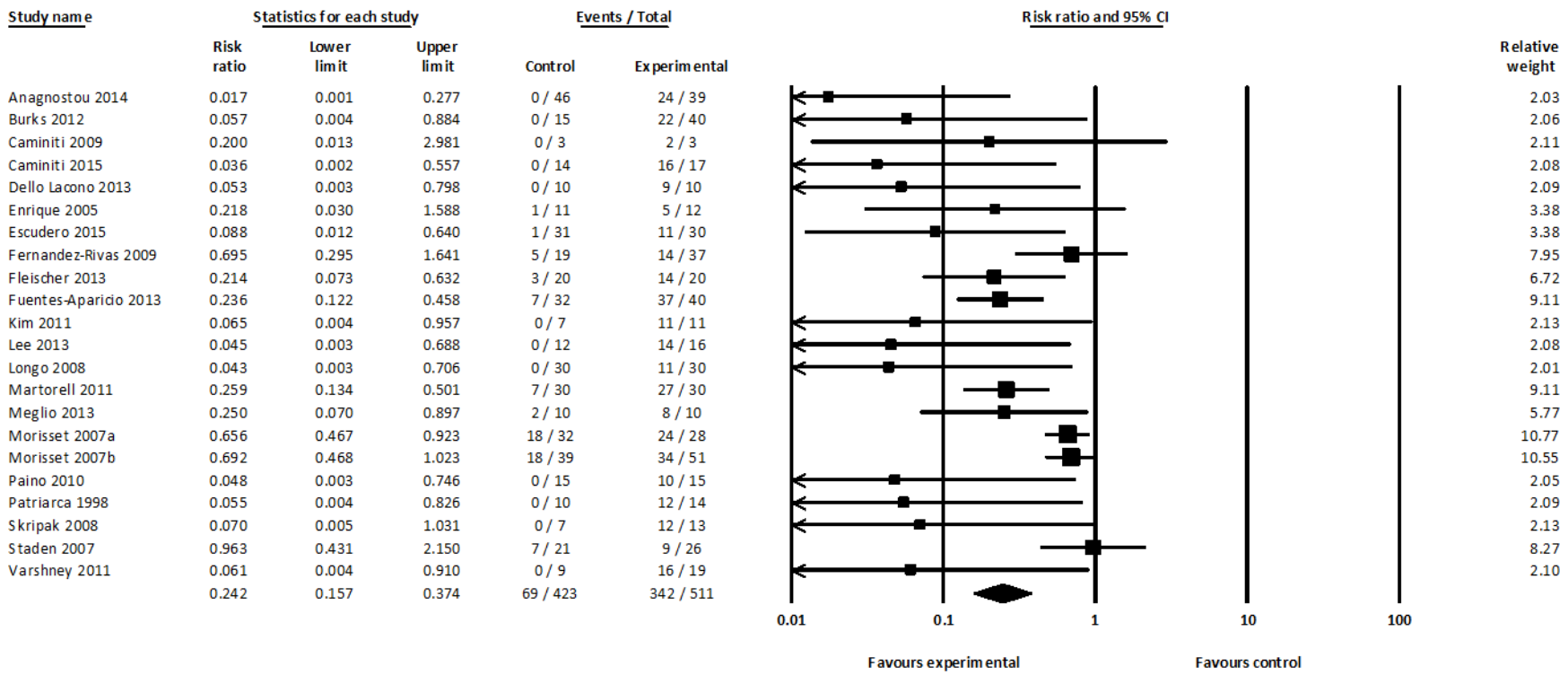

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Figure 2(c). Sensitivity analysis RR of desensitization after OIT or SLIT (only LRB and URB studies) (random-effects model)

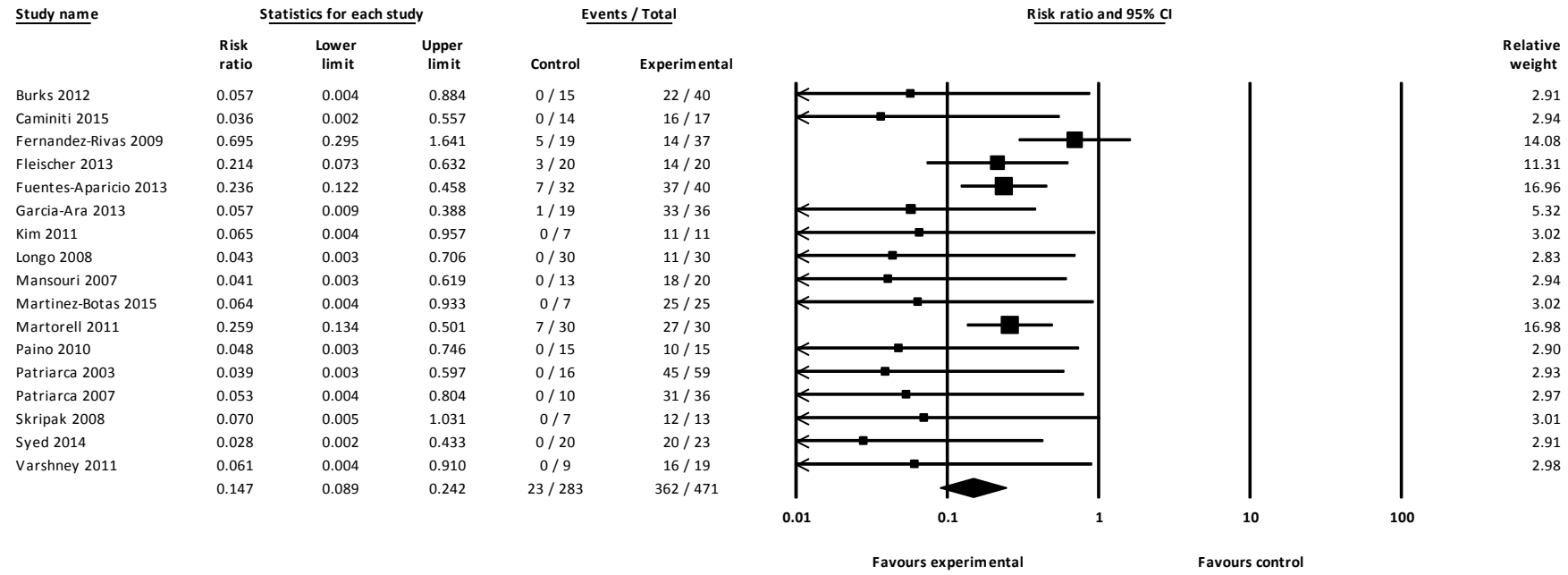

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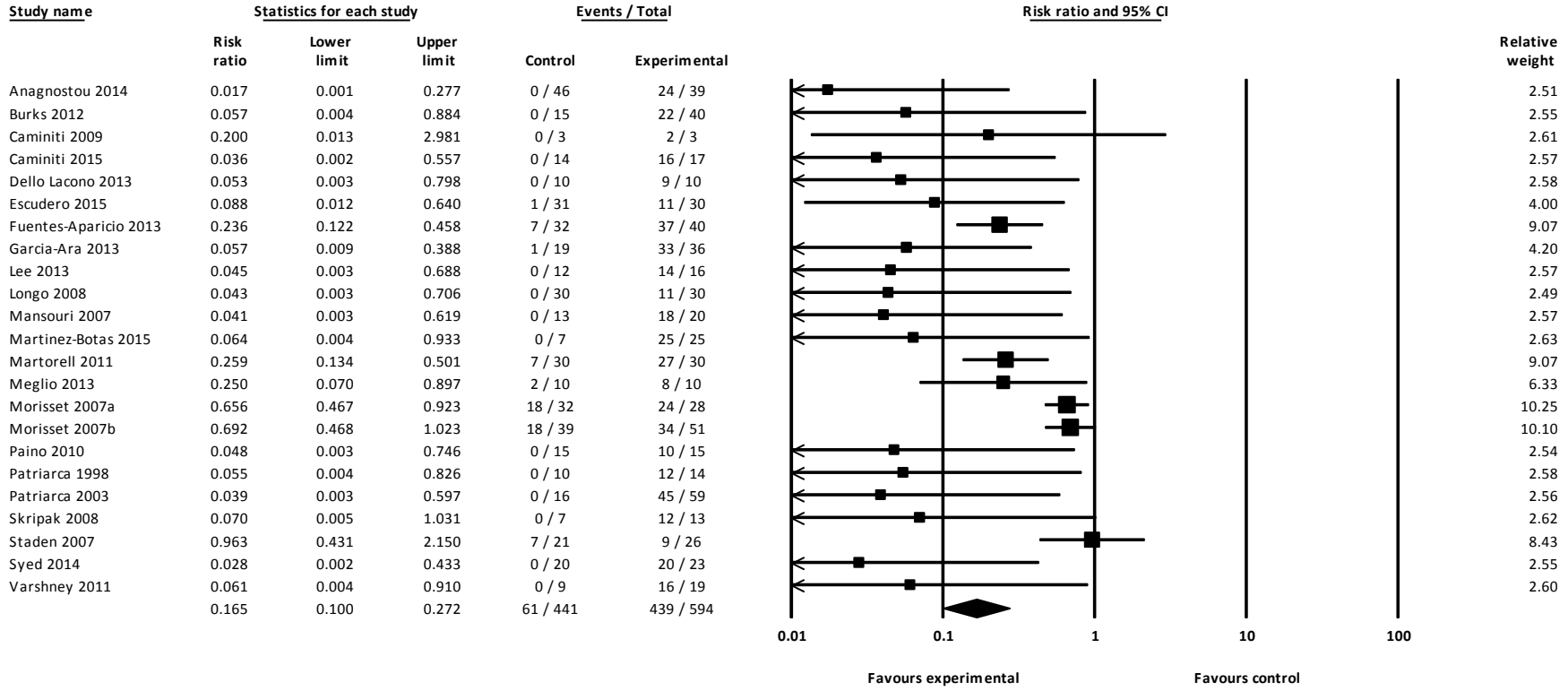
Figure 3. Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in OIT v. controls (random-effects model)



Heterogeneity: $\tau^2 = 0.27$; $\chi^2 = 23.38$, df = 16 (P<0.104); $I^2 = 31\%$;

Test for overall effect: Z = 7.53 (P<0.0001)

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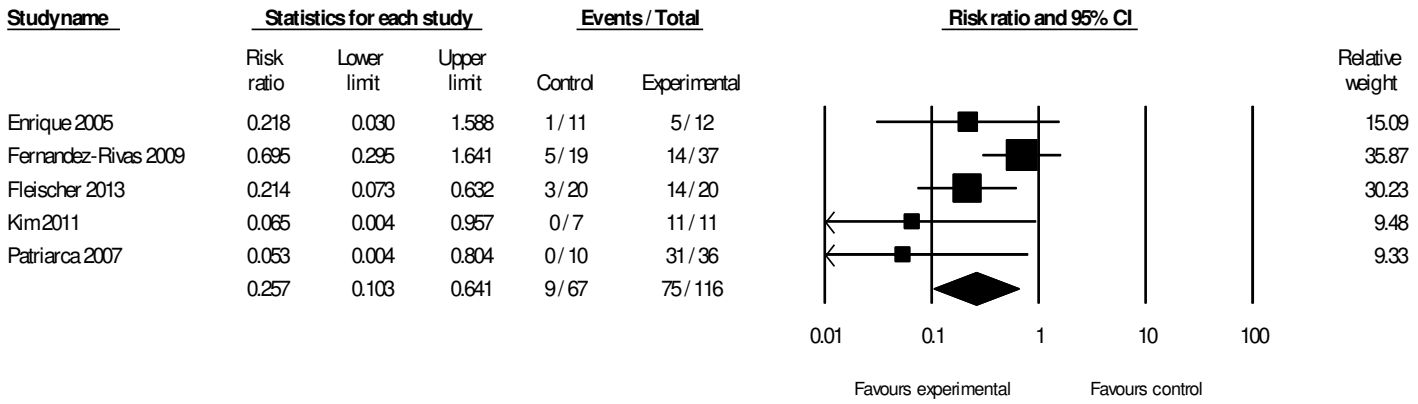
Figure 4. Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in SLIT v. controls (random-effects model)



Heterogeneity: $\tau^2 = 0.41$; $\chi^2 = 6.80$, df = 4 (P<0.147); $I^2 = 41\%$;

Test for overall effect: Z = 2.91 (P<0.004)

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Figure 5. Funnel plot showing: Log risk ratios of persistent food allergy after OIT or SLIT

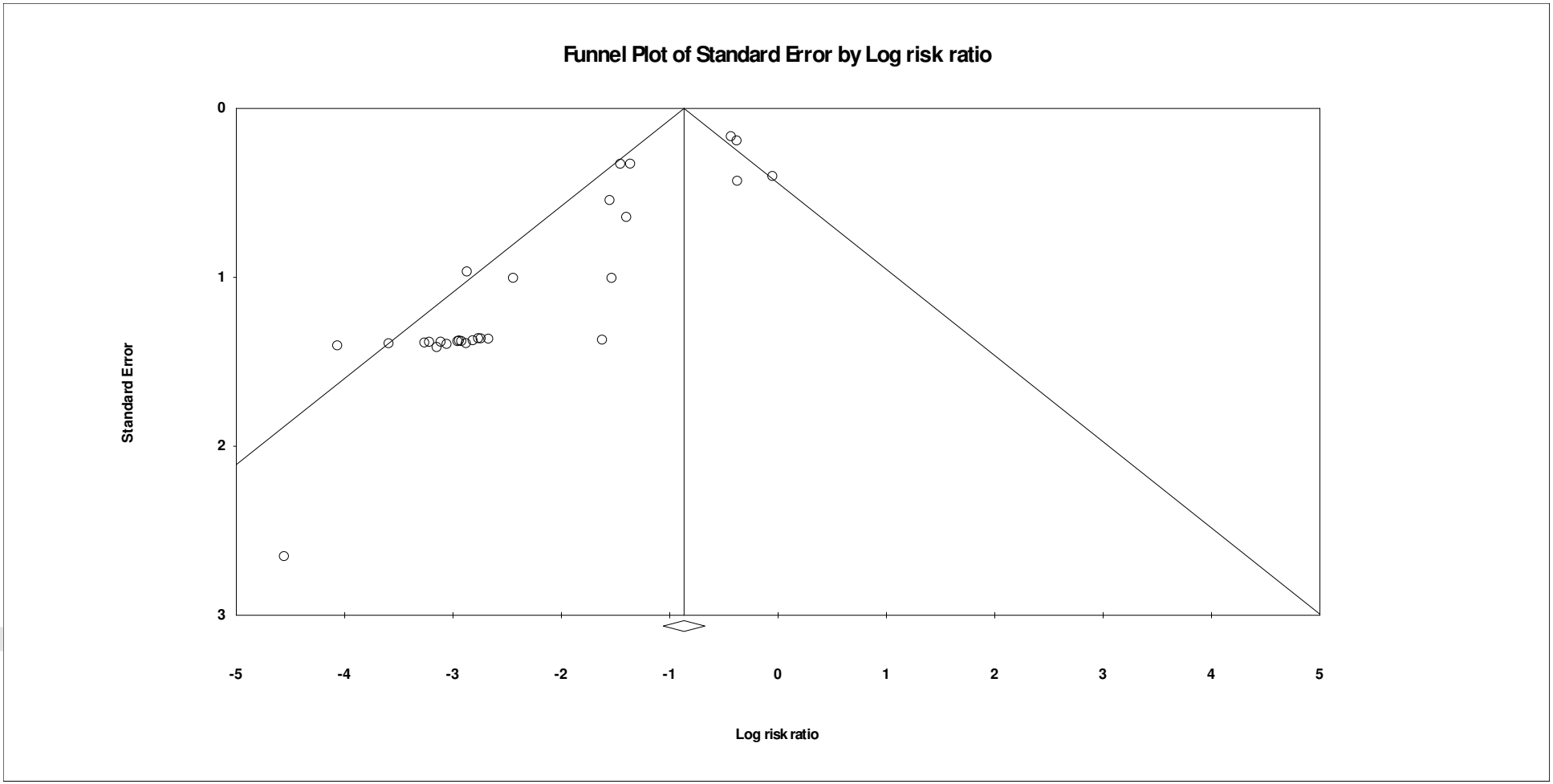

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Figure 6. Risk ratios (RR) of sustained unresponsiveness as assessed by double-blind placebo-controlled food challenge in OIT v. controls (random-effects model)

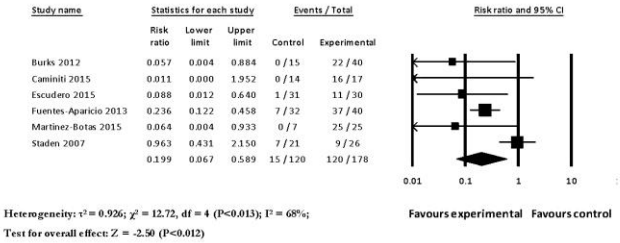

Figure 7. Sensitivity analysis RR of tolerance after OIT or SLIT (only RCTs) (random-effects model)

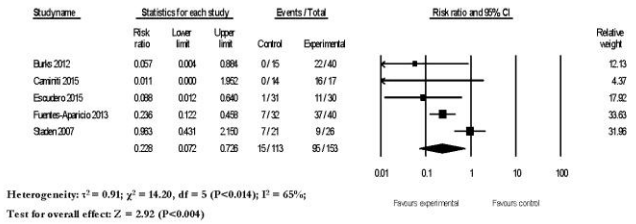

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Figure 8. Funnel plot showing: Log risk ratios of persistent food allergy after OIT or SLIT (only RCTs)

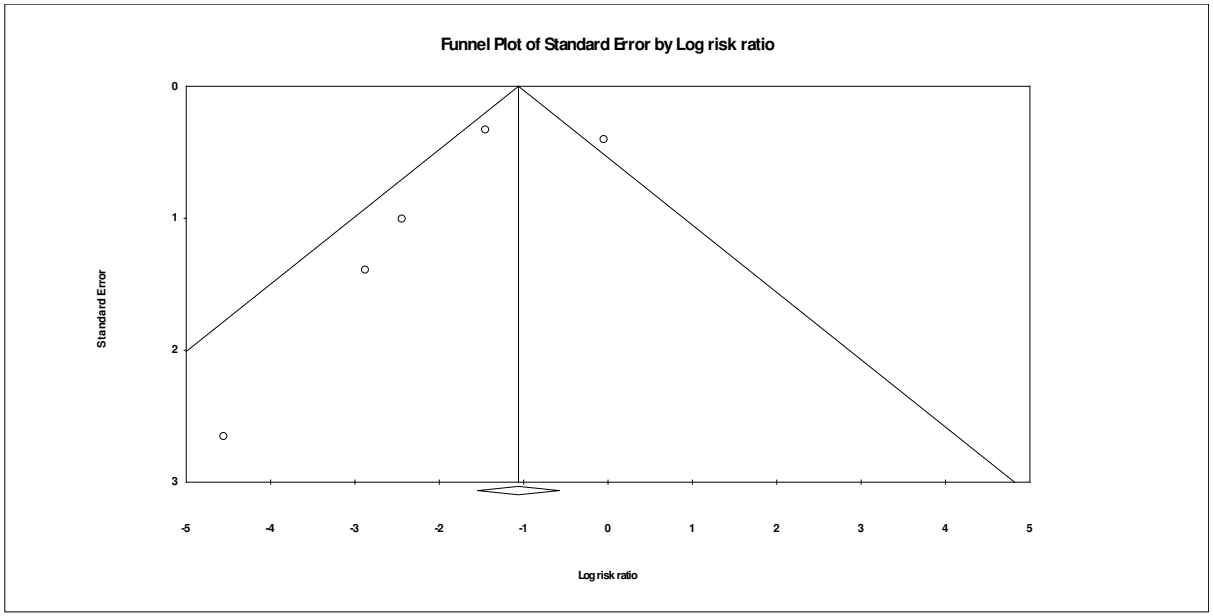

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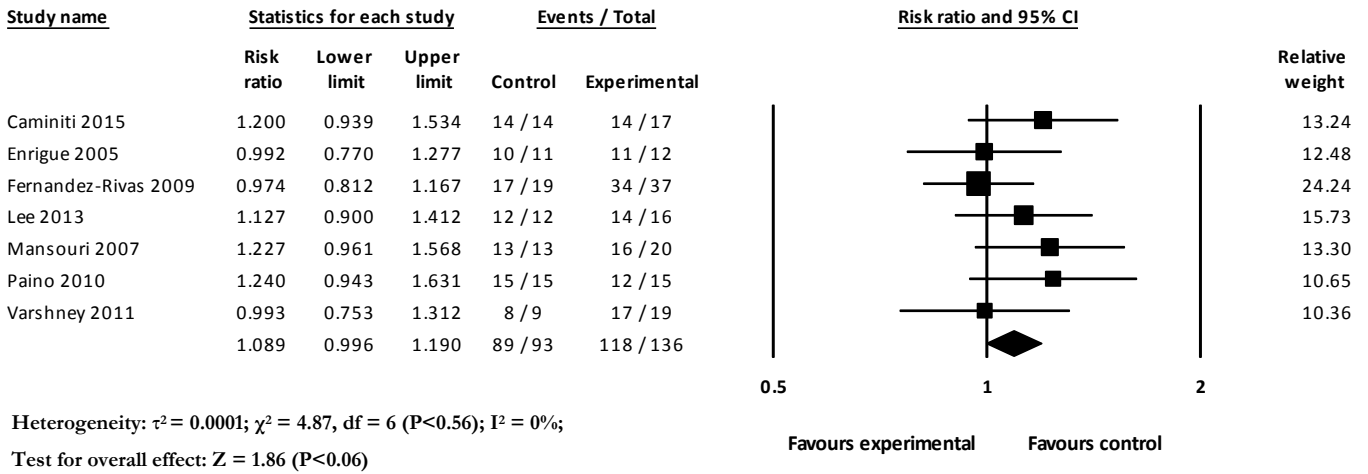
Figure 9. Safety data – absence of systemic reactions during OIT or SLIT for food allergy. RR, risk ratio (random-effects model)



Heterogeneity: $\tau^2 = 0.0001$; $\chi^2 = 4.87$, df = 6 (P<0.56); $I^2 = 0\%$;

Test for overall effect: Z = 1.86 (P<0.06)

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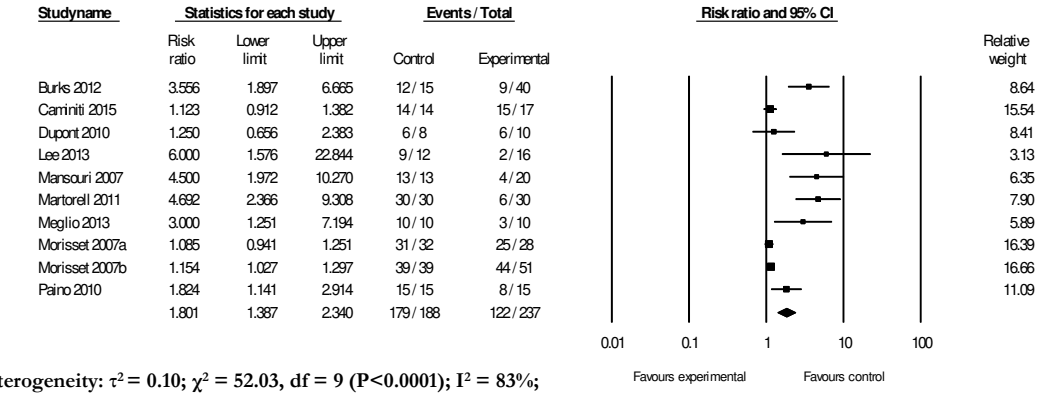
Figure 10. Safety data – absence of local reactions during OIT or EPIT for food allergy. RR, risk ratio (random-effects model)



Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 52.03$, df = 9 (P<0.0001); $I^2 = 83\%$;

Test for overall effect: Z = 4.41 (P<0.0001)

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Table 1. Description of the included studies (n=31)

Study (First author, year, country)	Food allergen (s)								Route AIT			Comparator		Evidence of allergy (mandatory inclusion criteria)					Clinical outcomes				
	Cow's milk	Hen's egg	Peanut	Hazelnut	Peach	Apple	Fish	Other(s)	OIT	SLIT	EPIT	Placebo	Routine care (food avoidance)	Clinical history	SPT &/ or sIgE	OFC	SBPCFC	DBPCFC	Desensitization	Sustained unresponsiveness	DR-QoL	Occurred AEs / medication use	
																						SRs	LRs
RCT (n=25)																							
Anagnostou, 2014, UK			X						X				X	X	X			X	X		X	X	X
Burks, 2012, USA		X							X			X		X	X				X	X		X	X
Caminiti, 2009, Italy	X								X			X		X	X			X	X			X	X
Caminiti, 2015; Italy		X							X			X		X	X			X	X	X		X	X
Dello Iacono, 2013, Italy		X							X				X	X	X			X	X			X	X
Dupont, 2010, France	X										X	X		X	X	X			X			X	X
Enrique, 2005, Spain				X						X[1]		X		X	X			X	X			X	X
Escudero, 2015, Spain		X							X				X	X	X			X		X		X	X
Fernandez-Rivas, 2009, Spain					X					X*		X		X	X			X	X			X	X
Fleischer, 2012, USA			X							X		X							X				
Fuentes-Aparicio, 2013, Spain		X							X				X	X	X	X			X	X		X	X
Kim, 2011, USA			X							X		X		X	X				X				
Lee, 2013, Korea	X								X				X	X	X			X	X			X	X
Longo, 2008, Italy	X								X				X	X	X			X	X			X	X
Martorell, 2011, Spain	X								X				X	X	X			X	X				X

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Study (First author, year, country)	Food allergen (s)								Route AIT			Comparator		Evidence of allergy (mandatory inclusion criteria)					Clinical outcomes				
	Cow's milk	Hen's egg	Peanut	Hazelnut	Peach	Apple	Fish	Other(s)	OIT	SLIT	EPIT	Placebo	care (food avoidanc						Desensitization	unresponsiveness	DR-QoL	Occurred AEs / medication use	
Meglio, 2013, Italy		X							X				X	X	X			X	X				X
Morisset, 2007, France^	X	X							X				X	X	X		X		X			X	X
Pajno, 2010, Italy	X								X			X		X	X			X	X			X	X
Patriarca, 1998, Italy	X	X				X	X		X				X	X	X			X	X				X
Salmivesi, 2012, Finland	X								X			X		X	X	X			X	X		X	X
Skripak, 2008, USA	X								X			X			X			X	X			X	X
Staden, 2007, Germany	X	X							X				X	X	X			X		X		X	X
Tang, 2015, Australia			X						X ¥			X		X	X			X	X	X		X	X
Varshney, 2011, USA			X						X			X		X	X				X			X	X
CCT (n=6)																							
García-Ara, 2013, Spain	X								X				X	X	X	X			X			X	X
Martınez-Botas, 2015, Spain	X								X				X	X	X			X	X	X		X	X
Mansouri, 2007, Iran	X								X				X	X	X			X	X			X	X
Patriarca, 2003, Italy	X	X	X		X	X	X	X**	X				X	X	X			X	X			X	X
Patriarca, 2007, Italy	X	X				X	X	X§		X*			X	X	X			X	X			X	X
Syed, 2014, USA			X						X				X	X	X			X		X		NR	NR

***AE**, adverse event; **AIT**, allergen specific immunotherapy; **DR-QoL**, disease related quality of life; **LR**, local reaction; **NR**, not reported; **OIT**, oral immunotherapy; **OFC**,* open food challenge; ***SLIT**, sublingual immunotherapy; **SR**, systemic reaction.*

¥ sublingual-discharge technique

* sublingual-swallow technique

** orange, corn, bean, lettuce

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§ wheat, bean

¥ AIT and probiotics

^ one report that included two independent randomized controlled trials on cows' milk and hens' eggs

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Supplementary materials: Appendices

Appendix 1: Search strategy

Appendix 2: Table S1. Detailed characteristics of included studies

Appendix 3: Table S2. Risk of bias assessment of RCTs

Appendix 4: Table S3. Risk of bias assessment of CCTs

Appendix 5: Additional forest plots (Figures S1 – S28)

1. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol. 2007;119(4):1016-8.
2. Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic. J Allergy Clin Immunol. 2007;120:491-503.
3. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69:62-75.
4. Kotz D, Simpson CR, Sheikh A. Incidence, prevalence, and trends of general practitioner-recorded diagnosis of peanut allergy in England, 2001 to 2005. J Allergy Clin Immunol. 2011;127:623-30.e1.
5. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh AoboTEFAAGG. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;2014(69):992-1007.
6. Prescott S, Pawankar R, Allen KJ, et al. A global survey of changing patterns of food allergy burden. World Allergy Organization Journal. 2013;6(1):21.
7. Sampson H, Mendelson L, Rosen J. Fatal and neat-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327(6):380-4.
8. Sampson H. Anaphylaxis and emergency treatment. Pediatrics. 2003;111((6 Pt 3)):1601-8.
9. DunnGalvin A, Dubois AE, Flokstra-de Blok BM, Hourihane JO. The effects of food allergy on quality of life. Chem Immunol Allergy 2015;101:235-52.
10. Primeau MN, Kagan R, Joseph L, Lim H, Dufreshne C, Duffy C, et al. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut allergic children. Clin Exp Allergy. 2000;30:1135-43.
11. Muraro A, Werfel T, Hoffman-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy Asthma Proc. 2014;69:1008-25.
12. Gupta R, Sheikh A, Strachan DP, Anderson HR. Time trends in allergic disorders in the UK. Thorax. 2007;62:91-6.
13. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Gareez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of

This article is protected by copyright. All rights reserved.

United Kingdom national anaphylaxis data, 1992-2012. J Allergy Clin Immunol. 2015;135:956-63.
14. Schofield A. A case of egg poisoning Lancet. 1908:i, 716.
15. Calderon MA, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: The meta-analyses. What have we Learned? Immunol Allergy Clin North Am. 2011;31:159-73.
16. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. Br J Nutr. 2014;111:12-22.
17. Nurmatov U, Venderbosch I, Devereux G, Simons FE, Sheikh A. Allergen-specific oral immunotherapy for peanut allergy. Cochrane Database Syst Rev. 2012;9: CD009014.
18. Dhami S, Nurmatov U, Pajno G, Fernandez Rivas M, Muraro A, Roberts G, et al. Allergen immunotherapy for IgE-mediated food allergy: protocol for a systematic review. Clinical & Translational Allergy. 2016 Jul 5:6:24.
19. Passalacqua G, Baena-Cagnani CE, Bousquet J, Walter Canonica G, Casalet T, Cox L, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language J Allergy Clin Immunology July 2013 http://www.jacionline.org/article/S0091-6749(13)00528-9/pdf. 2013.
20. WAOSISRGS hwaoAmMPDIFb-W-A-O-S-R-G-sp.
21. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration wwwcochrane-handbookorg. 2011.
22. Sterne J, Higgins J, Reeves BobotdgfA-N. A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24 September 2014. Available from http://www.riskofbias.info [assessed June, 2016]. 2014.
23. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014;383(9925):1297-304.
24. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367(3):233-43.
25. Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, et al. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. Allergy Asthma Proc. 2009;30(4):443-8.
26. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral immunotherapy for egg allergy: A double blind placebo controlled study, with post-desensitizazion follow-up. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70:99.
27. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. Pediatr Allergy Immunol. 2013;24(1):66-74.
28. Dupont C, Kalach N, Soulaines P, Legoue Morillon S, Piloquet H, Benhamou P. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. Journal of Allergy & Clinical Immunology. 2010;125(5):1165-7.
29. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: A randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. Journal of Allergy and Clinical Immunology. 2005;116(5):1073-9.
30. Escudero C, del Rio PR, Sanchez-Garcia S, Perez-Rangel I, Perez-Farinos N, Garcia-Fernandez C, et al. Early sustained unresponsiveness after short-course egg oral

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immunotherapy: a randomized controlled study in egg-allergic children. Clinical and Experimental Allergy. 2015;45(12):1833-43.
31. Fernandez-Rivas M, Fernandez SG, Nadal JA, de Durana M, Garcia BE, Gonzalez-Mancebo E, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009;64(6):876-83.
32. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. The Journal of allergy and clinical immunology [Internet]. 2013; 131(1):[119-27.e1-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/460/CN-00841460/frame.html.
33. Fuentes-Aparicio V, Alvarez-Perea A, Infante S, Zapatero L, D'Oleo A, Alonso-Lebrero E. Specific oral tolerance induction in paediatric patients with persistent egg allergy. Allergol Immunopathol (Madr). 2013;41(3):143-50.
34. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127(3):640-6.e1.
35. Lee JH, Kim WS, Kim H, Hahn YS. Increased cow's milk protein-specific IgG4 levels after oral desensitization in 7- to 12-month-old infants. Ann Allergy Asthma Immunol. 2013;111(6):523-8.
36. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343-7.
37. Martorell A, De la Hoz B, Ibanez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297-304.
38. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology [Internet]. 2013; 24(1):[75-83 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/238/CN-00968238/frame.html.
39. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol. 2007;39(1):12-9.
40. Pajno G, Caminiti L, Ruggeri P, de Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Annals of Allergy Asthma & Immunology. 2010;105:376-81.
41. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. Hepatogastroenterology. 1998;45(19):52-8.
42. Salmivesi S, Korppi M, Makela MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatrica, International Journal of Paediatrics [Internet]. 2013; 102(2):[172-6 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/754/CN-00912754/frame.html.
43. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154-60.
44. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy. 2007;62(11):1261-9.

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Accepted Article

45. Tang MLK, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. Journal of Allergy and Clinical Immunology. 2015;135(3):737-44.e8.
46. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654-60.
47. Garcia-Ara C, Pedrosa M, Belver MT, Martin-Munoz MF, Quirce S, Boyano-Martinez T. Efficacy and safety of oral desensitization in children with cow's milk allergy according to their serum specific IgE level. Ann Allergy Asthma Immunol. 2013;110(4):290-4.
48. Martinez-Botas J, Rodriguez-Alvarez M, Cerecedo I, Vlaicu C, dieguez MC, Gomez-Coronado D, et al. Identification of novel peptide biomarkers to predict safety and efficacy of cow's milk oral immunotherapy by peptide microarray. Clin Exp Allergy. 2015;45:1071-84.
49. Mansouri M, Movahhedi M, Pourpak Z, Akramian R, Shokohi Shormasti R, Mozaffari H, et al. Oral desensitization in children with IgE-mediated cow's milk allergy: a prospective clinical trial. Tehran University Medical Journal. 2007;65(5):11-8.
50. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, et al. Oral desensitizing treatment in food allergy: Clinical and immunological results. Alimentary Pharmacology and Therapeutics. 2003;17(3):459-65.
51. Patriarca G, Nucera E, Pollastrini E, Roncallo C, de Pasquale T, Lombardo C, et al. Oral specific desensitization in food-allergic children. Digestive Diseases and Sciences. 2007;52:1662-72.
52. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). J Allergy Clin Immunol. 2014;133(2):500-10.
53. Brozek J, Terracciano L, Hsu J, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clinical and Experimental Allergy. 2012;42:363-74.
54. Calvani M, Giorgio V, Sopo SM. Specific oral tolerance induction for food. A systematic review. Eur Ann Allergy Clin Immunol. 2010;42:11-9.
55. Fisher H, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance? Arch Dis Child. 2011;96:259-64.
56. Kurihara K. Immunotherapy for food allergy. Allergol. 2010;59:1-6.
57. Niggemann B, Staden U, Rolinck-Werninghaus C, et al. Specific oral tolerance induction for food allergy. Allergy. 2006;61:808-11.
58. Nowak-Wegrzyn A, Fiocchi A. Is oral immunotherapy the cure for food allergy? Curr Opin Allergy Clin Immunol. 2010;10:214-9.
59. Sheikh A, Nurmatov U, Venderbosch I. Oral immunotherapy for the treatment of peanut allergy: systematic review of six case series studies. Prim. 2012;21:41-9.
60. Sopo SM, Onesimo R, Giorgio V, et al. Specific oral tolerance induction (SOTI) in pediatric age: clinical research or just routine practice? Pediatr Allergy Immunol. 2010;21:e446-e9.
61. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective J Allergy Clin Immunol 2016 Aug 4. pii: S0091-6749(16)30531-0. doi: 10.1016/j.jaci.2016.05.027. [Epub ahead of print]

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